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(54) Title: 49 HUMAN SECRETED PROTEINS

(57) Abstract

The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

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nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 34

The computer algorithm BLASTX has been used to determine that the translation product of this gene shares sequence homology with, as a non-limiting example, the sequence accessible through the following database accession no. gi|57671 (all information available through the recited accession number is incorporated herein by reference) which is described therein as "ribonuclease inhibitor [Rattus norvegicus]." A partial alignment demonstrating the observed homology is shown immediately below.

```
>gi|57671 ribonuclease inhibitor [Rattus norvegicus] >pir|S20597|S20597
          ribonuclease inhibitor - rat
          Length = 456

  Plus Strand HSPs:

 Score = 519 (182.7 bits), Expect = 3.6e-49, P = 3.6e-49
 Identities = 123/325 (37%), Positives = 170/325 (52%), Frame = +1

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         E+ L  N+    A +  +L + + + TC +Q++  +N S  +A   +    LR   T+
S:    55 ELSLRTNE-LGDAGVGLVL-QGLQNPTCKIQKLSLQNCSLTEAGCGVLPDVLRSLSTLRE 112

Q:   817 LTLQGNDQ-DDMFPALCEVLRHPECNLRYLGLVSCSATTQQWADLSLALEVNQSLTCVNL 993
         L L  N   D+    LCE LR P+C L  L L  C+ T      L+  L V      + L
S:   113 LHLNDNPLGDEGLKLLCEGLRDPQCRLEKLQLEYCNLTATSCEPLASVLRVKPDFKELVL 172

Q:   994 SDNELLDEGAKLLYTTLRHPKCFLQRLSLENCHLTEANCKDLAAVLVVSRELTHLCLAKN 1173
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S:   233 KLGNTGIAALCSGLLLPSCRLRTLWLWDCDVTAEGCKDLCRVLRAKQSLKELSLAGNELK 292

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S:   293 DEGAQLLCESLLEPGCQLESLWVKTCSLTAASCPHFCSVLTKNSSLFELQMSSNPLGDSG 352

Q:  1534 VKMLFETLTCSSGTLRTLRLKIDDFND 1614
```

```
          V  L + L      LR L L   D  D
S:    353 VVELCKALGYPDTVLRVLWLGDCDVTD 379
```

The segment of gil57671 that is shown as "S" above is set out in the sequence listing as SEQ ID NO. 143. Based on the structural similarity these homologous polypeptides are expected to share at least some biological activities. Such activities are known in the art, some of which are described elsewhere herein. Assays for determining such activities are also known in the art, some of which have been described elsewhere herein.

Preferred polypeptides of the invention comprise a polypeptide having the amino acid sequence set out in the sequence listing as SEQ ID NO. 144 which corresponds to the "Q" sequence in the alignment shown above (gaps introduced in a sequence by the computer are, of course, removed).

It has been discovered that this gene is expressed primarily in the following tissues/cDNA libraries: Human Testes Tumor and to a lesser extent in Soares fetal liver spleen 1NFLS; NCI_CGAP_GCB1; Human Testes; Human Endometrial Tumor; Soares placenta Nb2HP; Soares infant brain 1NIB; 12 Week Old Early Stage Human, II; Human Uterine Cancer; Human Whole Six Week Old Embryo; Activated T-Cell (12hs)/Thiouridine labelledEco; Spleen, Chronic lymphocytic leukemia and Soares_placenta_8to9weeks_2NbHP8to9W.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 93 as residues: Asp-194 to Leu-199, Ile-206 to Pro-211, Glu-224 to Ser-229.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:44 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence

would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1978 of SEQ ID NO:44, b is an integer of 15 to 1992, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 35

The computer algorithm BLASTX has been used to determine that the translation product of this gene shares sequence homology with, as a non-limiting example, the sequence accessible through the following database accession no. gil2559012 (all information available through the recited accession number is incorporated herein by reference) which is described therein as "chaperonin containing t-complex polypeptide 1, beta subunit; CCT-beta [Homo sapiens]." A partial alignment demonstrating the observed homology is shown immediately below.

```
  >gi|2559012 (AF026293) chaperonin containing t-complex polypeptide 1, beta
              subunit; CCT-beta [Homo sapiens] >gi|2559012 (AF026293)
chaperonin
              containing t-complex polypeptide 1, beta subunit; CCT-beta
[Homo
              sapiens] >gi|4090929 (AF026166) chaperonin-containing TCP-1
beta
              subunit homolog [Homo sapiens] >sp|G4090929|G4090929
              CHAPERONIN-CONTAINING TCP-1 BETA SUBUNIT HOMOLOG.
              >sp|G2559012|G2559012 CHAPERONIN CONTAINING T-COMPLEX
POLYPEPTIDE
              1, BETA SUBUNIT. >gi|1871210 T-complex protein 1, Beta subunit
              (TCP-1-BETA) [Homo sapiens] (SUB 1-217)
              Length = 535

   Plus Strand HSPs:

 Score = 2610 (918.8 bits), Expect = 9.4e-271, P = 9.4e-271
 Identities = 525/535 (98%), Positives = 525/535 (98%), Frame = +2

Q:    92 MASLSLAPVNIFKAGADEERAETARLTSFIGAIAIGDLVKSTLGPKGMDKILLSSGRDAS 271
```

What Is Claimed Is:

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X, having biological activity;

(f) a polynucleotide which is a variant of SEQ ID NO:X;

(g) a polynucleotide which is an allelic variant of SEQ ID NO:X;

(h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;

(i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;

(c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(g) a variant of SEQ ID NO:Y;

(h) an allelic variant of SEQ ID NO:Y; or

(i) a species homologue of the SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15. A method of making an isolated polypeptide comprising:

(a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and

(b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

(a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

22. A method of identifying an activity in a biological assay, wherein the method comprises:

(a) expressing SEQ ID NO:X in a cell;

(b) isolating the supernatant;

(c) detecting an activity in a biological assay; and

(d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.

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Gly Met Lys Phe Leu Cys Glu Ala Leu Arg Lys Pro Leu Cys Asn Leu
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Arg Cys Leu Trp Leu Trp Gly Cys Ser Ile Pro Pro Phe Ser Cys Glu
    130                 135                 140

Asp Leu Cys Ser Ala Leu Ser Cys Asn Gln Ser Leu Val Thr Leu Asp
145                 150                 155                 160

Leu Gly Gln Asn Pro Leu Gly Ser Ser Gly Val Lys Met Leu Phe Glu
                165                 170                 175

Thr Leu Thr Cys Ser Ser Gly Thr Leu Arg Thr Leu Arg Leu Lys Ile
            180                 185                 190

Asp Asp Phe Asn Asp Glu Leu Asn Lys Leu Leu Glu Glu Ile Glu Glu
        195                 200                 205

Lys Asn Pro Gln Leu Ile Ile Asp Thr Glu Lys His His Pro Trp Glu
    210                 215                 220

Glu Arg Pro Ser Ser His Asp Phe Met Ile Xaa
225                 230                 235


<210> 94
<211> 9
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (9)
<223> Xaa equals stop translation

<400> 94
Ser Leu Phe Trp Gly Cys Pro Trp Xaa
  1               5


<210> 95
<211> 42
<212> PRT
<213> Homo sapiens

<220>
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Glu Ser Leu Trp Val Lys Thr Cys Ser Leu Thr Ala Ala Ser Cys Pro
            260                 265                 270

His Phe Cys Ser Val Leu Thr Lys Asn Ser Ser Leu Phe Glu Leu Gln
        275                 280                 285

Met Ser Ser Asn Pro Leu Gly Asp Ser Gly Val Val Glu Leu Cys Lys
    290                 295                 300

Ala Leu Gly Tyr Pro Asp Thr Val Leu Arg Val Leu Trp Leu Gly Asp
305                 310                 315                 320

Cys Asp Val Thr Asp
                325


<210> 144
<211> 325
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (16)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 144
Glu Met Gly Leu Ala Ile Asn Asp Ser Phe Leu Ser Ala Ser Leu Xaa
  1               5                  10                  15

Arg Ile Leu Cys Glu Gln Ile Ala Ser Asp Thr Cys His Leu Gln Arg
            20                  25                  30

Val Val Phe Lys Asn Ile Ser Pro Ala Asp Ala His Arg Asn Leu Cys
        35                  40                  45

Leu Ala Leu Arg Gly His Lys Thr Val Thr Tyr Leu Thr Leu Gln Gly
    50                  55                  60

Asn Asp Gln Asp Asp Met Phe Pro Ala Leu Cys Glu Val Leu Arg His
65                  70                  75                  80

Pro Glu Cys Asn Leu Arg Tyr Leu Gly Leu Val Ser Cys Ser Ala Thr
                85                  90                  95

Thr Gln Gln Trp Ala Asp Leu Ser Leu Ala Leu Glu Val Asn Gln Ser
            100                 105                 110

Leu Thr Cys Val Asn Leu Ser Asp Asn Glu Leu Leu Asp Glu Gly Ala
        115                 120                 125
```

```
Lys Leu Leu Tyr Thr Thr Leu Arg His Pro Lys Cys Phe Leu Gln Arg
    130                 135                 140

Leu Ser Leu Glu Asn Cys His Leu Thr Glu Ala Asn Cys Lys Asp Leu
145                 150                 155                 160

Ala Ala Val Leu Val Val Ser Arg Glu Leu Thr His Leu Cys Leu Ala
                165                 170                 175

Lys Asn Pro Ile Gly Asn Thr Gly Val Lys Phe Leu Cys Glu Gly Leu
            180                 185                 190

Arg Tyr Pro Glu Cys Lys Leu Gln Thr Leu Val Leu Trp Asn Cys Asp
        195                 200                 205

Ile Thr Ser Asp Gly Cys Cys Asp Leu Thr Lys Leu Leu Gln Glu Lys
    210                 215                 220

Ser Ser Leu Leu Cys Leu Asp Leu Gly Leu Asn His Ile Gly Val Lys
225                 230                 235                 240

Gly Met Lys Phe Leu Cys Glu Ala Leu Arg Lys Pro Leu Cys Asn Leu
                245                 250                 255

Arg Cys Leu Trp Leu Trp Gly Cys Ser Ile Pro Pro Phe Ser Cys Glu
            260                 265                 270

Asp Leu Cys Ser Ala Leu Ser Cys Asn Gln Ser Leu Val Thr Leu Asp
        275                 280                 285

Leu Gly Gln Asn Pro Leu Gly Ser Ser Gly Val Lys Met Leu Phe Glu
    290                 295                 300

Thr Leu Thr Cys Ser Ser Gly Thr Leu Arg Thr Leu Arg Leu Lys Ile
305                 310                 315                 320

Asp Asp Phe Asn Asp
                325


<210> 145
<211> 535
<212> PRT
<213> Homo sapiens

<400> 145
Met Ala Ser Leu Ser Leu Ala Pro Val Asn Ile Phe Lys Ala Gly Ala
  1                 5                  10                  15

Asp Glu Glu Arg Ala Glu Thr Ala Arg Leu Thr Ser Phe Ile Gly Ala
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